

Appln. No. 10/763,190
Amdt. dated September 6, 2005
Reply to Office action of April 5, 2005

Amendments to the Specification:

Please delete the title on page 1 and replace with the following amended title:

~~DIAGNOSTIC MARKERS FOR THERAPEUTIC TREATMENT~~METHOD FOR
MONITORING THE EFFECTIVENESS OF AN AGENT INTERACTING WITH THE
A3 ADENOSINE RECEPTOR

Please replace paragraph [0039] with the following amended paragraph:

[0039] **Figs. 5a-5b** show the correlation between tumor size and the level of regulatory elements in ~~colon~~ carcinoma melanoma cells, wherein Fig. 5a presents tumor size after 15 days of daily treatment with IB-MECA of mice inoculated with ~~B16~~ B16-F10 melanoma cells, while Fig. 5b presents the modulation of cell growth regulatory proteins (PKAc, PKB/Akt, GSK-3 β , β -catenin cyclin D1 ,c-myc and NF- κ B) in the tumor lesions described in Fig. 5a (left prior to treatment with A3AR agonist; right after treatment with A3AR agonist).

Please replace paragraph [0077] with the following amended paragraph:

[0077] To test whether protein expression was modulated due to degradation and re-synthesis, the cells were exposed for 180 minutes to IB-MECA in the presence of MG132 (protein degradation inhibitor) and cycloheximide (protein

synthesis inhibitor). Indeed, MG132 prevented A3AR down-regulation and cycloheximide inhibited receptor up-regulation, illustrating that following internalization, receptor degradation and re-synthesis took place (Fig. 4b). Moreover an increase in mRNA expression level was observed, suggesting that a *de novo* synthesis of A3AR had occurred (Fig. 4e). The specificity of this response was demonstrated by MRS1523 which reversed the increase in mRNA expression.

Please delete the heading before paragraph [0080], that begins "**Example 4: Monitoring ...**"

Please delete paragraph [0080].

Please delete the heading before paragraph [0081] and replace with the following amended heading:

Example 54: Monitoring Change of Expression of Biological Markers in Prostate Carcinoma (PC-3)

Please delete the heading following paragraph [0081] and replace with the following amended heading:

Example 65: Monitoring Changes of Expression Level of Biological Markers in Colon Carcinoma Cells as a Result of IB-MECA Administration

Please add a paragraph number to the paragraph following the heading beginning "Example 5: ..." as follows:

[0081.1] The effect of IB-MECA on key proteins downstream to A3AR activation in HCT-116 human colon carcinoma cells was also examined in a manner similar to that performed with melanoma cells (see above). Fig. 7 presents Immunoblot

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analysis of protein extracts derived from colon carcinoma cell, wherein treatment with IB-MECA (right lane) caused down-regulation of PKAc, PKB/Akt, β -catenin, c-myc and cyclin D1 and NF- κ B and up-regulation of GSK-3 β expression level as compared to control (left lane). These results conform with the results obtained with melanoma, and prostate cancer cells and presented hereinabove and support the notion that determination of the expression level of these regulatory elements may function as biological markers for disease states.

Please delete the heading before paragraph [0083] and replace with the following amended heading:

| **Example 76: Monitoring Expression of Key Proteins Downstream to A3AR Activation by IB-MECA Treatment in Melanoma Cells**

Please delete the heading before paragraph [0084] and replace with the following amended heading:

| **Example 87: IB-MECA Inhibits Colon Carcinoma Development in Mice and Down-Regulates Expression of Biological Markers**

Please delete the heading before paragraph [0085] and replace with the following amended heading:

| **Example 98: Monitoring the Expression Level of Biological Markers in Clinical Treatment**

Please delete the heading before paragraph [0092] and replace with the following amended heading:

Example 109: Detection of A3AR Receptor on Human Neutrophils

Please replace paragraph [0092] with the following amended paragraph:

[0092] 10×10^6 neutrophil cells isolated from 20 ml of human blood were incubated for 15 minutes with 0.01 mM or 10 mM of ~~CF101~~-IB-MECA at 37°C. The cells were collected by centrifugation and washed with PBS. RNA was extracted from the cells by using TRI-reagent (Sigma). RNA level was quantified using spectrophotometer and 1 mg from each sample were subjected to RT-PCR using SuperScript One Step RT-PCR with Platinum Taq (Invitrogene), as described above in section E., by using the set No II as primers for amplification of 361 bp fragment. RT-PCR products were detected by electrophoresis and the size was verified by comparing with known RNA.

Please delete the heading before paragraph [0094] and replace with the following amended heading:

Example 110: Modulation of Inflammatory Response and Expression of A3AR and Some Downstream Proteins by IB-MECA

Please replace paragraph [0094] with the following amended paragraph:

[0094] Adjuvant induced arthritis (AIA) was induced in rats as described above. Rats were treated orally twice daily with either (i) vehicle (these rats serving as control), (ii) 10 μ g/kg IB-MECA or with (ii) the specific A3AR agonist

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antagonist MRS 1220 followed 30 minutes later by IB-MECA. The mice were sacrificed on day 28 for histological scoring and measurement of signaling proteins and TNF- α .